Study Protocol and Statistical Analysis Plan

Study Title: Efficacy of Intermittent Tiotropium in Early Childhood Wheezing

Trial number: NCT03199976

Version: 4.2 / 1.11.2018

Online Publication: https://doi.org/10.1542/peds.2021-055860

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BACKGROUND

Wheezing in early childhood

During the first three years of life, up to 30% of all children suffer from episodic wheeze or shortness of breath [Martinez et al. 1995, Skytt et al. 2012], i.e. asthmatic bronchitis, usually induced by viral respiratory infections. The condition causes significant burden to the affected children and their families, including need for acute health care visits, hospitalizations, and costs related to parents' days off from work. However, early childhood wheezing is rarely associated with eosinophilic inflammation of the airways seen in asthma [Saglani et al. 2005], and only one third of these infants and toddlers with wheezing will actually develop asthma [Martinez et al. 1995, Skytt et al. 2012]. Because the condition is very heterogeneous, short-acting beta-agonists are recommended as a monotherapy for symptoms unless there are at least four physician-confirmed episodes of wheeze or shortness of breath, or three episodes plus risk factors according to the modified asthma predictive index [Guilbert et al. 2004] criteria [Finnish Current Care Guidelines for Lower respiratory tract infections in children and for Asthma; http://www.kaypahoito.fi/web/english/home]. Thereon, inhaled corticosteroids or leukotriene modifiers are usually administered as intermittent or regular medication to prevent symptoms. However, these medications used to control asthma have, at its best, only modest effect on early childhood wheezing [Castro-Rodriguez et al. 2009]. In addition, daily use of inhaled corticosteroids may affect growth [Kelly et al. 2012]. Accordingly, there is a current need for new therapeutic agents to treat young children with recurrent troublesome lung symptoms.

Effects of tiotropium in the airways

In viral-induced wheeze, increased parasympathetic nerve activity results in increased acethylcholine release from nerve endings [Quizon et al. 2012]. Acethylcholine interacts with muscarinic receptors of the airways causing smooth muscle contraction, mucus secretion and vasodilation [Quizon et al. 2012]. Tiotropium bromide (Spiriva®) is an inhaled anticholinergic agent which selectively binds to muscarinic receptors of the airways [Quizon et al. 2012, Heredia et al. 2009] and by preventing the acetylcholine function, achieves mild bronchodilatation and decrease in mucus secretion from the submucosal glands [Quizon et al. 2012, Heredia et al. 2009]. When added to an inhaled glucocorticoid, tiotropium provided significantly superior results in comparison with doubling the dose of inhaled glucocorticoid, both with regard to improvement in symptoms and lung function [Peters et al. 2010]. In addition, inhaled tiotropium has been shown a protective effect against methacholine-induced bronchoconstriction in asthmatic patients with mild to moderate airways hyperresponsiveness in a short-term follow-up [Terzano et al. 2004].

Tiotropium may also have anti-inflammatory effect by binding to the muscarinic receptors of the airway epithelial and inflammatory cells [Quizon et al. 2012]. In line, adding salmeterol and tiotropium to fluticasone reduced exhaled nitric oxide levels significantly, although the dose of fluticasone was reduced to half from baseline [Fardon et al. 2007].

Pharmacokinetics of tiotropium

Tiotropium has a long duration of action, making once-a-day dosing possible [see Summary of Product Characteristics (SPC) for Spiriva Respimat 2.5 µg; https://www.medicines.org.uk/emc]. Approximately 40% of the inhaled dose is deposited in the lungs, the target organ, and the remaining amount is deposited in the gastrointestinal tract. However, due to electrical charge, tiotropium is poorly absorbed by the gastrointestinal tract, bioavailability of oral solutions being 2-3%. Of the inhaled tiotropium, 33% of the dose reaches the systemic circulation, and maximum tiotropium plasma concentrations are observed 5-7 minutes after inhalation. The drug has a plasma protein binding of 72%, and studies in rats have shown that tiotropium does not pass the blood-brain barrier. Following inhalation, the effective half-life of the drug is 27-45 hours. Majority (74% of the drug in healthy volunteers) of the tiotropium that reaches systemic circulation is excreted unchanged in urine. Consequently, tiotropium has low systemic bioavailability and few systemic side-effects [Heredia et al. 2009, Befekadu et al. 2014, Rodrigo and Castro-Rodriguez 2015].

Interaction with other drugs and overdosage of tiotropium

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, and anti-IgE treatment without clinical evidence of drug interactions [see SPC for Spiriva Respimat 2.5 µg; https://www.medicines.org.uk/emc]. Use of long-acting beta agonists or inhaled corticosteroids has not been found to alter the exposure to tiotropium. The co-administration of tiotropium bromide with other anticholinergic containing drugs has not been studied and therefore is not recommended. Overdose of tiotropium may lead to undesired anticholinergic effects. However, single inhaled dose of up to 340 µg tiotropium bromide in healthy volunteers caused no systemic anticholinergic adverse effects [see SPC for Spiriva Respimat 2.5 µg; https://www.medicines.org.uk/emc]. Additionally, no relevant adverse effects, beyond dry mouth/throat and dry nasal mucosa, were observed following 14-day dosing of up to 40 µg tiotropium inhalation solution in healthy volunteers with the exception of pronounced reduction in salivary flow from day 7 onwards [see SPC for Spiriva Respimat 2.5 µg; https://www.medicines.org.uk/emc].

Tiotropium in preclinical studies

According to SPC for Spiriva Respimat 2.5 ug [see https://www.medicines.org.uk/emc], in preclinical safety studies, many effects observed in animals - including reduced food consumption, inhibited body weight gain, dry mouth and nose, reduced lacrimation and salivation, mydriasis and increased heart rate - can be explained by the anticholinergic properties of tiotropium bromide. In repeated dose toxicity studies following effects were also observed: mild irritancy of the respiratory tract in rats and mice evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder in rats. In juvenile rats exposed from postnatal day 7 to sexual maturity, the same direct and indirect pharmacological changes were observed as in

the repeat-dose toxicity studies as well as rhinitis. No systemic toxicity was noted and no toxicologically relevant effects on key organ development were seen.
Harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide has not been teratogenic in rats or rabbits. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at any dosage.
The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity was observed at local or systemic exposures more than five-fold the therapeutic exposure. Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.

Tiotropium in clinical studies in adults

According to the records of PubMed (see www.ncbi.nlm.nih.gov/pubmed), since 1993 until the end of June 2015, there were 257 reports published on clinical trials with tiotropium in chronic obstructive pulmonary disease (COPD) and 26 reports on clinical trials with tiotropium in asthma. In a recent review with a meta-analysis of 13 randomized double-blind placebo-controlled trials on tiotropium in asthma, tiotropium was considered noninferior to salmeterol and superior to placebo in patients with asthma inadequately controlled with inhaled corticosteroids with or without salmeterol [Rodrigo and Castro-Rodriguez 2015]. The improvement of lung function and the reduction of asthma exacerbations were considered as major benefits of tiotropium in patients with uncontrolled asthma [Rodrigo and Castro-Rodriguez 2015]. There were no significant differences in incidences of serious adverse events between those receiving tiotropium (1.9%) and those receiving conventional therapy (2.1-2.5%) [Rodrigo and Castro-Rodriguez 2015].

Tiotropium studies in children

In Clinical Trial Registries (see www.clinicaltrials.gov and www.clinicaltrialsregister.eu), there are altogether 7 clinical trials on tiotropium as add-on therapy in asthma in children: one study including children aged 1 to 5 years (trial number: NCT01634113), three studies including children aged 6 to 11 years (trials: NCT01634139, NCT01634152, NCT01383499), and three studies including adolescents (trials: NCT01257230, NCT01122680, NCT01277523). Results on efficacy and safety issues have recently been published for asthmatic adolescents (trials number: NCT01122680, NCT01257230) [Vogelberg et al. 2014, Hamelmann et al. 2016], and children aged 6 to 11 years (trial number: NCT01383499) [Vogelberg et al. 2015], and children aged 1 to 5 years (trial number: NCT01634113) [Vrijlandt et al. 2018]. In addition, tiotropium has been investigated in children suffering from cystic fibrosis [Konstan et al. 2015, Ratjen et al. 2015], and in children with postinfectious bronchiolitis obliterans [Teixeira et al. 2013].

Safety of tiotropium in clinical studies in adults

The main side effect of tiotropium reported in clinical studies is dryness of the mouth in <2% of patients [Befekadu et al. 2014, Kerstjens et al. 2012, Kerstjens et al. 2015]. In a 48-week

intervention with tiotropium in severe asthma poorly controlled with standard combination therapy in 912 adults, drug-related adverse events were similar in the tiotropium group (5.7%) and in the placebo group (4.6%). Serious adverse events were reported for 8.1% of the patients in the tiotropium group and 8.8% in the placebo group; drug-related cardiac events being rare (0.4%), including no deaths [Kerstjens et al. 2012]. In a recent report combining data on two 24-week trials on tiotropium in moderate asthma, serious adverse events occurred in 2% of the 2100 patients included [Kerstjens et al. 2015]. Incidence of serious adverse events was similar between the intervention groups, and none of the life-threatening serious adverse events occurring in four patients was regarded as drug-related, and there were no deaths [Kerstjens et al. 2015].

Efficacy and safety of tiotropium in children

This far, the evidence of efficacy and safety of tiotropium in asthmatic children has been mainly limited on ongoing clinical trials. In a recently published report including 105 adolescent patients with symptomatic asthma despite inhaled corticosteroids [Vogelberg et al. 2014], tiotropium 5 µg was regarded superior to placebo with regard to improvement of lung function, whereas treatment differences between tiotropium 2.5 µg and placebo, and tiotropium 1.25 µg and placebo did not reach statistical significance. Overall incidence of adverse events was balanced across treatment groups with no dose-dependence [Vogelberg et al. 2014]. Four serious adverse events -- none of which were life-threatening or fatal -- were experienced by two patients (1.3%) during the study: pre-syncope in a patient receiving tiotropium 5 µg, and asthma exacerbations, H1N1 influenza and mycoplasmal pneumonia occurred in a patient receiving tiotropium 1.25 µg. None of these serious adverse events were considered as to be related to the study medication. Another study on tiotropium in asthmatic adolescents [Hamelmann et al. 2016] reports similar rates (1.4-2.2%) of serious adverse events, none of which was considered drug-related. Serious undesirable effects consistent with anticholinergic effects including urinary retention, constipation, intestinal obstruction, or acute glaucoma, were reported in none of these studies.

The results of the trial including children aged 6 to 11 years old with moderate asthma (trial number: NCT01383499) were recently published [Vogelberg et al. 2015]. It was reported that tiotropium as add-on therapy to medium-dose inhaled corticosteroids, with or without a leukotriene modifier, was efficacious in children with symptomatic asthma, and the safety and tolerability of tiotropium were comparable with those of placebo, with no serious adverse events and no events leading to discontinuation [Vogelberg et al. 2015].

The preliminary results of the tiotropium trial including asthmatic children from age of 1 year on (trial number: NCT01634113) [Vrijlandt et al. 2018], showed no differences in safety profiles between those receiving tiotropium 5 µg, those receiving tiotropium 2.5 ug, and those receiving placebo. No serious adverse events occurred in either of the tiotropium groups during the 12-week intervention period, whereas 3 of the 34 children receiving placebo experienced a serious adverse event (i.e. appendicitis, bronchopneumonia and exacerbation of asthma, viral upper respiratory infection), requiring hospital admission. Among other adverse events, there were no undesirable anticholinergic effects, or no differences in occurrence of adverse events between the intervention groups [Vrijlandt et al. 2018].

In addition, an earlier clinical trial on a short-acting non-selective anticholinergic agent, ipratropium bromide, in 25 children aged 5 to 15 years with severe acute asthma, found no significant differences in side effects between the study groups [Reisman et al. 1988]. Moreover, there is a recent report on tiotropium in cystic fibrosis, including 24 children aged 5 to 11 years, and 24 patients aged 12 years or older [Konstan et al. 2014]. Only two of these patients with cystic fibrosis experienced a serious adverse event, neither of which was considered drug-related [Konstan et al. 2014].

OBJECTIVE

The primary AIM of the study is

1) to find out the effect of intermittent tiotropium bromide and salbutamol as needed (TBS) versus intermittent fluticasone propionate and salbutamol as needed (FPS), or solely, salbutamol as needed (SA) on episode-free days in infants and toddlers with recurrent episodes of wheeze and/or shortness of breath.

   Episode-free days are defined as those days during which there are no symptoms of wheeze and/or shortness of breath, no unscheduled medical visits for wheeze and/or shortness of breath, and no use of rescue or supplementary controller medications [Guilbert et al. 2006].

The secondary AIMS of the study are

to find out the effect of TBS versus FPS or SA treatment on

1) number of unscheduled physician visits for episodes of wheeze and/or shortness of breath,
2) need for bronchodilative medication,
   and to evaluate
3) the safety of TBS versus FPS or SA treatment by paying attention to possible adverse events during treatment

in infants and toddlers with recurrent episodes of wheeze and/or shortness of breath.

STATISTICAL POWER OF THE STUDY

The primary endpoint of the study is the proportion (%) of episode-free days in the TBS group, compared with the SA, after a 48-week intervention period. To ensure a 80% power to detect a 15% difference (corresponding to 1 day per week) in episode-free days between the treatment groups, at least 64 children per group were required, assuming a standard deviation of 27% for symptom-free days seen in a previous study [Bisgaard et al. 2006], and a possible drop-out percent of 20%. The calculation is based to reject the primary hypothesis with 5% significancy level.

STATISTICAL ANALYSIS PLAN

Normality of the distribution of continuous variables are to be evaluated by Shapiro-Wilk test. The overall difference between the treatment groups is to be evaluated by using either analysis of variance, Kruskal-Wallis, log-rank, chi-squared, or Fisher's exact tests. Pairwise analyses are to be performed by using Mann-Whitney U, chi-squared, or Fisher's exact tests. Bonferroni correction is to be applied in pairwise analyses by multiplying each P-value by 3. Influence of confounding factors on the primary outcome is to be assessed by conducting the two-way factorial analysis of variance. $P<0.05$ is to be considered statistically significant. All study participants are to be included in safety analyses, and those with diary data available are to be included in primary analysis. All analyses are to be performed as intention-to-treat. IBM SPSS Statistics (version 22.0; Armonk, NY, US) is to be used for all analyses.

RESEARCH METHODS AND MATERIAL, ETHICAL ISSUES

Inclusion criteria:

1. Children at the age of 6 to 35 months.
2. Two to four physician-confirmed episodes of wheeze and/or shortness of breath.
3. Parents/legal representatives with sufficient written and spoken skills in Finnish language

Exclusion criteria:

1. Birth before 36^{th} week of gestation.
2. Suspected/diagnosed chronic parenchymal lung disease or a structural airway defect, or a history of thoracotomy with pulmonary resection.
3. A history of congenital or acquired heart disease, including any unstable or life-threatening cardiac arrhythmia.
4. Constipation with a need of regular medication, or a diagnosed/suspected structural defect in the gastrointestinal tract.
5. A history of malignancy, or other significant chronic disorder, disease, or defect.

Study population and study design

195 consecutive patients will be recruited in the study. Before enrolment, respiratory infections should be treated, and significant thoracic anomalies should be excluded by taking a chest X-ray scan. Background information is questioned as follows: gestational stature, birth weight and length, ethnic background, allergy to food and inhaled allergens diagnosed or strongly suspected by a physician, respiratory symptoms, wheezing episodes confirmed by a physician, other significant illnesses or diagnoses, operations, medication, atopic diseases in family members, smoking and pets at home, moist or mould problems at home.

The study children will be randomized into three groups. One third of the patients (SA group, n=65) will receive inhaled salbutamol (Ventoline Evohaler® 0.1 mg/dose), i.e. rescue medication, to be used 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath via a plastic spacer, Babyhaler®, during the whole study (i.e. SA group). One third of the patients (FPS group, n=65) will be randomized to receive fluticasone propionate (Flixotide Evohaler® 125 µg/dose), to be given 125 µg twice a day via Babyhaler®, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and in addition, inhaled salbutamol (Ventoline Evohaler® 0.1 mg/dose), i.e. rescue medication, to be used 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath via Babyhaler®, during the whole study. One third of the patients (TBS group, n=65) will be randomized to receive tiotropium bromide (Spiriva Respimat® 2.5 µg/dose), to be given 5 µg once a day via AeroChamber Plus®, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and in addition, inhaled salbutamol (Ventoline Evohaler® 0.1 mg/dose), i.e. rescue medication, to be used 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath via AeroChamber Plus®, during the whole study. The intervention will last for 48 weeks. The drugs and the plastic spacers will be supplied by the pharmacy of Helsinki University Hospital.

The parents are taught to keep diary on wheeze and shortness of breath, and on the use of rescue and intervention medication. The use of medications is controlled by measuring weights of the inhalators at the end of the 48-week intervention. After the 48-week intervention period, medication for episodes of wheeze and shortness of breath will be planned individually and the patients are remitted back.

Control phone calls by a research nurse will take place at 4, and 8 weeks from the beginning of the intervention. The control visits will take place at 12, 24, 36, and 48 weeks from the beginning of the intervention. In all cases, the first (week 0) and last (week 48) visits are to be organized at HUH Skin and Allergy Hospital. For those subjects living in Helsinki, the control visits at 12, 24, and 36 weeks will take place at HUH Skin and Allergy Hospital, and for those living in surrounding municipalities of Helsinki, the control visits (at 12, 24, and 36 weeks) will take place at a local hospital (Jorvi, Porvoo, or Hyvinkää), i.e. nearest hospital of the living place of the study subject.

Adverse events requiring unscheduled medical attendances, as well as serious adverse events requiring hospital admission are to be charted. In case the study patient is diagnosed a chronic illness needing regular controls and physician care, the investigator will evaluate the situation and considers, case by case, a withdrawal of the patient from the study. However, hospitalization for wheezing or shortness of breath, or administration of drugs other than the interventional ones are not considered as indications for the discontinuation of the study, as these occasions are regarded as normal occurrences in early childhood wheezing illnesses. Per oral or inhalant corticosteroids may be used in any of the study groups as additional medications if they meet the criteria stated in the Finnish Current Care Guidelines for asthma in children [see http://www.kaypahoito.fi/web/english/home].
In case of the discontinuation, wheezing episodes of the study children will be treated according to the Finnish Current Care Guidelines for asthma in children [see http://www.kaypahoito.fi/web/english/home].

Blood and urine samples

A venous blood sample is a part of the routine diagnostic evaluation and is drawn from all children (5-15 ml of blood, <1% of the circulating blood volume) during the first visit, and at the 48-week visit. In addition, a urine sample is collected during the first visit, and at the 48-week visit. Following parameters are to be analysed: total blood cell count, serum allergen-specific immunoglobulin E concentrations for a mixture of inhalant and food allergens (Phadiatop combi®). In addition, serum 1-2 ml and urine 10 ml are taken for storage for analysis of immunological markers in future.

Handling of data

Detailed personal information on the study patients is collected by interviewing the caregivers during the study visits and by phone calls by study investigators and registered study nurses, and by collecting data from patient files in medical records. No data enabling identification of the patient is included in the case report forms or electronic files including the study data. IBM SPSS version 22.0 is used for electronic handling of the study data, including saving and analysing study material in an electronic form. The case report forms are saved in lockers in locked storage rooms. Only certain named investigators, a study monitor, and study nurses have access to the case report forms and the electronic study data. Whenever any changes are performed in the case report forms, the changes are to be verified by a signature. In case the changes are made in electronic data, a new file is to be created to document changes in the data.

Discontinuation of the study leads to the intention-to-treat analysis of the collected case-specific data.

The study files and data are preserved until the study children reach school age, in order to give an opportunity for a final evaluation of the study patients' respiratory state. However, such long-term evaluations reaching school age are out of the scope of the present research protocol.

Insurances

Injuries related to the actions of investigating physicians or nurses, or injuries related to the study investigations or measurements are to be covered with a patient insurance.
Pharmaceutical injuries insurance covers possible unexpected study drug-related adverse events.

Ethical considerations

To date, repeated episodes of wheezing or other persistent troublesome lung symptoms are treated only with short-acting beta-2-agonists unless there are multiple physician-confirmed episodes and risk factors present [Finnish Current Care Guidelines for Lower respiratory tract

infections in children and for Asthma; http://www.kaypahoito.fi/web/english/home]. In the study protocol, an earlier start of an intermittent controller therapy for those randomized to TBS or FPS groups, as well as intensive follow-up of symptoms for all intervention groups can be seen as advantages of the study.

Possible unexpected drug-related adverse events can be seen as possible disadvantages of the study; however, occurrence of drug-related adverse events is attempted to be minimized by including conditions that may increase the risk for drug-related adverse events in the exclusion criteria.

Approval of the study protocol is to be asked from the National Committee on Medical Research Ethics (TUKIJA), and written informed consent is to be obtained from each patient's legal representative prior to randomization. The trial is to be conducted in accordance with the guiding principles of the Declaration of Helsinki, and in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and local regulations.

Any substantial amendments in the study protocol are to be announced in a written form (Substantial Amendment Notification Form) both to the Finnish Medicines Agency (Fimea) and to TUKIJA. In addition, any changes among study personnel (i.e. investigators) and/or study sites are to be announced to Fimea and TUKIJA.

IMPLEMENTATION: TIMETABLE, BUDGET, DISTRIBUTION OF WORK

Timetable

Recruitment of patients was started in April 2016. Based on the number of referrals of patients with wheezing episodes or other persistent troublesome lung symptoms to the hospital district of Helsinki and Uusimaa, it is estimated that the last patient will be recruited in the study at the end of year 2019. The last follow-up visit will be timed at the end of year 2020. Thereafter, all the study data will be saved in an electronic form, analysed, and published in international forums.

Budget

The budget (approximately 300 000 euros) includes the salary for a post-doctoral researcher, Anne Kotaniemi-Syrjänen, working in the Paediatric Unit of HUH Skin and Allergy Hospital. In addition, the budget includes costs of medicines for the intervention, costs of materials for office work, costs for laboratory measurements, costs for services like proofreading of the manuscripts, and consulting of a professional statistician and a computer scientist. Study visits at weeks 12 and 36 are regarded as additional visits not included in the follow-up schema presented in Finnish Current Care Guidelines for Lower respiratory tract infections in children and for Asthma (see http://www.kaypahoito.fi/web/english/home). In addition, for those children living in surrounding municipalities of Helsinki, the first and last study visits are

regarded as nonconventional visits causing extra mobility for them. The costs of these two additional visits and the nonconventional visits are included in the study budget. The salary for the post-doctoral researcher and other costs are to be covered with personal grants and project grants from research funds and foundations until the end of year 2019. Thereafter costs are to be planned to be covered with grants from research foundations.

Tasks for the study members and collaborators

Principal Investigator, MD Mika Mäkelä, Paediatrician and Paediatric Allergologist, Professor in Clinical Allergology, is in charge for designing the study, follow-up of the patients, and reporting.
MD Anne Kotaniemi-Syrjänen, Paediatrician, is in charge for designing the study, recruiting the patients, follow-up, and reporting.
MD Anna Pelkonen, Paediatrician and Paediatric Allergologist, is in charge for designing the study, follow-up of the patients, and reporting.
MD Kristiina Malmström, Paediatrician and Paediatric Allergologist, is in charge for designing the study, recruiting the patients, follow-up, and reporting.
MD Pekka Malmberg, Clinical Physiologist, is in charge for designing the study, and reporting.
MD Timo Klemola, Paediatrician, Paediatric Allergologist and Paediatric Gastroenterologist, is in charge for recruiting the patients, follow-up, and reporting.
MD Henrikka Aito, Paediatrician, is in charge for recruiting the patients, follow-up, and reporting.
MD Petri Koponen, Paediatrician, is in charge for recruiting the patients, follow-up, and reporting.
MD Outi Jauhola, Paediatrician, is in charge for recruiting the patients, follow-up, and reporting.
MD Eero Rahiala, Paediatrician, is in charge for screening the emergency department patients, and reporting.
PhD Seppo Sarna, Professor in Biometrics, is in charge for the statistical evaluation of the study data.
RN Anssi Koivuselkä is in charge for recruiting the patients, control phone calls, and follow-up.

Monitoring of the study

Monitoring of the study will be organized before the start of the recruitment of the study patients, and thereafter once a year during the recruitment and follow-up, and at the end of the study. Monitoring will be accomplished by Monitoring Services of Clinical Research Institute HUCH Ltd.

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